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Report, End of Year

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To summarize all the work performed at the end of
the year and, therefore, the contract period.

CONTRACT NAS -9- 16225

REPORT, END OF YEAR

DEVELOPMENT OF W-Ta GENERATOR

E.R. SQUIBB & SONS

New Technology Representative: R.D. Neirinckx

A. INTRODUCTION

The purpose of this research program is to further develop the existing 178W-178Ta generator (1) and to evaluate alternative adsorbents, preferably inorganic materials, as supports for the generator.

During the first half year, combinations of non-complexing eluents and a variety of adsorbents, both inorganic and organic, were evaluated. Some of these adsorbents were synthetic, such as chelate resins that could be specific for tungsten.

In the second half of the year, the stress was mainly on the use of complexing eluents because of the high affinity of hydrous oxides for tantalum, on the synthesis of chelate resins and on the use of novel techniques (electrolytic) to solve the tantalum-adsorption problem.

B. MATERIALS AND METHODS

The following chromatographic inorganic adsorbents were supplied by Applied Research (Brussels, Belgium); hydrous titanium oxide, titanium oxide hydrogen peroxide hydrate, hydrous zirconium oxide, hydrous ferric oxide, hydrous stannic oxide, polyantimonic acid, silicic acid, hydrous chromium oxide, hydrous manganese dioxide, zirconium phosphate, tin phosphate, Phomix (20% ammonium phosphotungstate in zirconium phosphate), Siphozir (zirconium phosphate-silicate), chromium phosphate, titanium phosphate, molybdenyl ferrocyanide, zirconium ferrocyanide, ferric ferrocyanide and K-Co ferrocyanide. Alumina was obtained from Woelm (Eschwege, Germany), Tungsten carbide, non-chromatographic, was obtained from Pfaltz and Bauer (Stamford, Conn.) Tungsten disulfide was obtained from Alfa-Ventron (Danvers, Mass.). Bio-Rex G and Bio-Rad AG 3x4 A were obtained from Bio-Rad (Richmond, Cal.), Amberlite CG-400 from Mallinckrodt (St. Louis, Mo.) and diethyl aminoethyl cellulose DE-32 from Whatman (Clifton, N.J.).

Other inorganic materials were synthesized by us. They included tungstic acid (WO_3); CaF_2 and SrF_2 -coated Al_2O_3 ; anhydrous SnO_2 , TiO_2 , SiO_2 , CrO_3 , MnO_2 , Tin phosphate, zirconium phosphate, titanium phosphate, molybdenyl ferrocyanide, zirconium ferrocyanide and ferric ferrocyanide. Tungstic acid adsorbent was produced by heating WO_3 with a B_2O_3 flux to $1,200^\circ\text{C}$, cooling the melt to 800°C at a rate of $2^\circ\text{C}/\text{hour}$ and then uncontrolled to room temperature. CaF_2 and SnF_2 coated Al_2O_3 were prepared by treatment with a NaF solution of a Al_2O_3 adsorbent that had been saturated with Ca^{2+} or Sr^{2+} by equilibration of the adsorbent with concentrated solutions of CaCl_2 or SrCl_2 , respectively.

The anhydrous inorganic materials were prepared by heating the corresponding aqueous materials in a nickel crucible until H_2O -evolution ceased. A SnO_2 -adsorbent with lower adsorptivity was obtained by saturating the adsorption sites with $\text{Ca}(\text{II})$. The synthetic chelate resins included a pyrogallol-formaldehyde resin, which had been reported earlier (2) and experimental resins formed by copolymerisation of alphanitrobenzoin oxime or AMHOP (anti-1,5-di(p-methoxyphenyl)-1-hydroxylamine-3-oximino-4-pentene) with formaldehyde only the pyrogallol-formaldehyde resin is presently in a form suitable for column use.

Most development work has involved the measurement by batch equilibration of the K_D values of W and Ta between these adsorbents and various mobile phases of interest. The first adsorbent was pre-equilibrated three times with the liquid phase, and the supernate decanted. The batch equilibration was carried out using 100 mgr of adsorbent and 5 grams of mobile phase, to which a ^{178}W - ^{178}Ta mixture was added. The two phases were then shaken for 5 minutes by means of a Hematec Aliquot mixer. After centrifugation, samples from each phase were analyzed for ^{178}W and ^{178}Ta by means of a $\text{Ge}(\text{Li})$ detector coupled to an ND60 γ -spectrophotometer.

^{178}Ta was quantitated using its 93 kev gamma-ray. After correction for physical decay, the K_D -values for tantalum were calculated as described previously (3). ^{178}W is quantitated after both fractions are allowed to decay for 90 minutes and by counting the equilibrium activity of ^{178}Ta associated with the ^{178}W . The K_D -values are calculated as for tantalum.

The following non-complexing eluents were evaluated: 10^{-3}N HCl , H_2O , 0.1N NaOH , 0.25% $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$, 0.7% NaCl + 0.2% NaHCO_3 , 0.9% NaCl and 0.1% NaHSO_3 .

As complexing eluents citric acid, sodium citrate solutions, sodium fluoride solutions of varying acidity, EDTA and ascorbic acid were evaluated.

C. SUMMARY OF RESULTS AND DISCUSSION

I. K_D -determinations

a. Non-complexing eluents/Inorganic adsorbents

A radioisotope generator should display a strong adsorption of the mother isotope (W-178) and a weak adsorption for the daughter isotope (Ta-178).

A summary of the results with the evaluated inorganic adsorbent/non-complexing eluent combinations is given in Tables 1-3. Table 1 summarizes the results for adsorbents that have a high affinity for tantalum, Table 3 for the adsorbents that have a low affinity for tungsten and Table 3 for the adsorbents that have a high affinity for both tungsten and tantalum. As can be seen from these tables, the use of non-complexing eluents combined with inorganic adsorbents does not lead to an acceptable W-178/Ta-178 generator system.

TABLE 1

K_D of tantalum between various eluents and inorganic adsorbents with a high affinity for tantalum

Absorbent/ Mobile phase	$10^{-3}N$ HCl	H ₂ O	0.1N NaOH	0.25% PO ₄ ³⁻	0.7% NaCl 0.2% NaHCO ₃	0.9% NaCl	0.1% NaHSO ₃
TiO ₂	>200	>150	>30	>60	>80	>150	>300
SnO ₂ (CaCl ₂)	>200		>40	>200		>250	
Zr (ferrocy)	>250		>50				
Ni (ferrocy)	>200		>70				
Ti (ferrocy)	>300		>90				
K-Co (ferrocy)	>300		>180	>60		>70	
SnO ₂ (heated)	>60		>45				
SnO ₂ /CaCl ₂	>200		>40	>200			>250
WS ₃	>100						>100

TABLE 2

K_D values of W between various eluents and inorganic adsorbents with low affinity for tungsten

Adsorbent/ Mobile phase	$10^{-3}N$ HCl	H ₂ O	0.1N NaOH	0.25% PO ₄ ³⁻	0.7% NaCl 0.2% NaHCO ₃	0.9% NaCl	0.1% NaHSO ₃
SnO ₂	30	68	41	6	5	120	18
SiO ₂	27		7			3	
Neutral Al ₂ O ₃	30		6	8			
CrO ₃	2		2	3		3	
Zr-phosph	15	44	16	89	55	96	55
Sn-phosph	4	14	8	51	28	78	35
tungsten carbide	5		1	36	6	12	24
Phomix		34	17				
Siphozir		53	12				
Cr-phosph	3		4				
Cu-ferrocy	8		10				
MoO ₂ (ferrocy)	7						
TiO ₂	95	110	10	17	21		
Al ₂ O ₃ /CaF ₂	3		3	6		28	
Al ₂ O ₃ /SrF ₂	6		8	15		20	
WS ₃			2	24	2		6

TABLE 3

K_D values for W and Ta between various eluents and inorganic adsorbents with a high affinity for both elements

Adsorbent/ Eluent	$10^{-3}N$ HCl	H ₂ O	0.1N NaOH	0.25% PO ₄ ³⁻	0.7% NaCl + 0.2% NaHCO ₃	0.9% NaCl	0.1% NaHSO ₃
TiO ₂ ·H ₂ O ₂ / K _{DW}	>2500	>500	59	>1300	>1300	>1300	>1000
K _{DTa}	>200	>400	>140	>300	>300	>350	>300
Fe ₂ O ₃ /K _{DW}	>2400	>1000		>125		>800	>800
K _{DTa}	>500	>250		>125		>200	>170
Sb ₂ O ₅ /K _{DW}	>250			>600	>900	>900	>800
K _{DTa}	>100			>200	>200	>200	>200
MnO ₂ /K _{DW}	2100		95	800		5600	
K _{DTa}	>350		>200	>300		>800	
Ti-phosph/ K _{DW}	275		140	380		1100	
K _{DTa}	>150		>110	>200		>200	
Fe(III)/ ferrocyanide/ K _{DW}	1500		125	470		800	
K _{DTa}	>140		>140	>90		>60	
ZrO ₂ /K _{DW}	>100	>400				>250	>250
K _{DTa}	>200	>100				>50	>50

b. Non-complexing eluents/organic adsorbents

1. Commercially-available adsorbents

The organic adsorbents AG 3x4A, CG-400 and DE-32 all have a high affinity for tantalum.

The K_D -value of W between 0.01N HCl, 0.1N HCl or 0.5N HCl and Bio-Rex 9 was 71, 61 and 35, respectively. This adsorbent had a low affinity for tantalum.

2. Synthetic results

The K_D -values for W and Ta between the synthetic chelate resin pyrogallol-formaldehyde and aqueous solutions of differing pH are summarized in Table 4.

TABLE 4

K_D values for W and Ta between pyrogallol-formaldehyde and aqueous phases of variable pH

pH mobile phase	1	2	3	4	5	6	7	11
K_{DW}	10	8	8	6	80	70	60	60
K_{DTa}	>50	>50	>50	>50	>50	>50	>50	>50

3. Anhydrous adsorbents

It is well known that metal oxides have a high affinity for elements which hydrolyze easily.

The influence of hydration water of the adsorbents on the adsorption of tantalum-178 was evaluated by substitution of CH_3OH for H_2O in desorption studies from ZrO_2 with 10^{-2} - 10^{-5} N HCl.

Using aqueous solutions, the % Ta-desorption was 1%-10% with 10^{-5} N - 10^{-2} N HCl. Using methanolic solutions, the yields were 70-90% with 10^{-5} - 10^{-2} N HCl, 70% with pure methanol. The K_{DW} was 6,000-2,500 for 10^{-5} - 10^{-2} N HCl.

This indicates that reaction of the highly activated tantalum species, formed by W-178 decay react with water to yield strongly-adsorbing species. The adsorption characteristics of dehydrated metal oxides was studied next. The K_D values for W between the hydrous oxides or the heated "anhydrous" oxides and various aqueous solutions are given in Table 5. Adsorption as well as desorption values are given from the HCl 0.1N + H_2O_2 0.1% solution.

TABLE 5

K_{DW} between hydrous and anhydrous adsorbents and various aqueous eluents

Adsorbent	K_{DW}		K_{DW} 5% glucose solution	1% Sodium tetraphenyl borate solution
	ADS. HCl 0.1N + H_2O_2	DES. 0.1%		
hydrous TiO_2	22,000	17,500	10,000	>20,000
TiO_2 heated	6,000	11,000	9,000	14,000
hydrous Zr-Si- PO_4	1	190		
Zr-Si- PO_4	1	150		
hydrous Ti-phosph	11	120	400	1,500
Ti-heated	4	65		
hydrous SnO_2	610	11,000	3,800	8,000
SnO_2 heated	160	280		
hydrous ZrO_2	825	1,550	1,500	7,000
ZrO_2 heated	dissolves			
hydrous SiO_2	7	17		
SiO_2 heated	9	27		

In nearly all cases the anhydrous adsorbents have less affinity for tungsten. However, in all cases the K_D 's for tantalum were higher than for tungsten, and as such none of the heated adsorbents is suitable as a support for a W-178/Ta-178 generator when used with a non-complexing eluent.

When using the non-complexing eluents of all the previous studies, most of the evaluated adsorbents display a strong affinity for tantalum. The balance of the solid phases adsorb tungsten too weakly to be of practical value.

The reason for the strong tantalum binding may be that most of the adsorbents are either metal oxides or phosphates. The tantalum 5d-orbitals overlap strongly with oxygen 2p-orbitals to give substantial π -bonding. The initial protonated species of the resultant tantalum oxides can expand their coordination sphere by coordinating water molecules. Since most of our adsorbents studied are hydrates, this could have lead to the strong tantalum binding. Tantalum -178, separated from W-178 by using an earlier-published procedure (1) was used to evaluate whether the binding of tantalum onto the adsorbents is irreversible. A phosphate-buffered solution of tantalum-178 was equilibrated with ZrO_2 , the K_D measured and the adsorbent subsequently reequilibrated with fresh eluent. The K_D for the desorption was compared with the adsorption values as a function of the phosphate buffer concentration. For sodium phosphate concentrations between 0.1% and 0.25% the K_{DTa} for adsorption was 4, while by desorption it was 1,600. This demonstrates the irreversibility of the tantalum adsorption or the slow kinetics of its desorption. Since the tantalum -178 is carrier-free it is very unlikely that polymeric species, e.g., $Ta_6O_{18}^{6-}$ are involved in the binding.

The problems encountered may also be caused by the chemical composition of the W-178 compound loaded onto the adsorbents. Isoelectronic transition of the W-178 probably does not break any chemical bonds between the daughter isotope Ta-178 and the atoms or groups of the molecule. Most of the experiments have been carried out with WO_4^{2-} so that the resultant tantalum species may be expected to be oxygenated. Therefore, experiments with fluoride-complexes of tungsten were carried out. It is also planned to evaluate other W-complexes. The choice of the complexant should be such that the evolving tantalum-complex is stable and possibly without affinity for inorganic adsorbents. These tungsten-complexes will only be stable in solutions containing the complexant.

b. Complexing eluents/inorganic adsorbents

1. Altered adsorbents

Citrate was evaluated first as a complexant for W and Ta. To insure that sufficient complexant be available, the studied inorganic adsorbents were heated with an aqueous

saturated sodium citrate solution before use in K_D determinations. Equilibration was then carried out between W-178 containing 1% sodium citrate solutions and the respective pretreated adsorbents. The K_D -values for W are summarized in Table 6.

TABLE 6

Adsorbent*	K_{DW}
Phozir A	<1
Ti-phosphate (anhydrous)	<1
TiO ₂ (anhydrous)	60
TiO ₂	<1
SnO ₂	<1
Ti-phosphate	<1
SnO ₂ (anhydrous)	<1

* pretreated with citrate

The adsorption of W was negligible in nearly all cases, which makes these pretreated adsorbents unacceptable for the W-178/Ta-178 generator.

2. Commercially available adsorbents

The influence of the addition of complexants to the eluents on the adsorption of tungsten on the inorganic adsorbents was studied.

(1) Citric acid

0.01% citric acid was added to various eluents used with ZrO₂ and pertitanic acid. The results are shown in Table 7.

TABLE 7

Eluent	K_{DW} on	
	SrO ₂	Sb ₂ O ₅
10 ⁻³ N HCl	>100	>250
10 ⁻³ N HCl + citric acid	500	30
Saline 0.9%	>250	>900
Saline + citric acid	60	150
H ₂ O	>400	
H ₂ O + citric acid	340	

Addition of citric acid generally lowered tungsten adsorption, but in all cases the K_{DTa} was higher than K_{DW} .

(11) Ascorbic acid

Increasing amounts of ascorbic acid were added to 10⁻⁴N HCl eluent in combination with ZrO₂ or pertitanic acid. For ascorbic acid concentrations between 0 and 0.05% the percent tantalum eluted from ZrO₂ or pertitanic acid was constant and was 95% by adsorption

and 10% by desorption for SnO_2 , and 70% by adsorption and 0.1% by desorption for pertitanic acid.

(111) EDTA

Addition of 0.05% EDTA to 10^{-4}N HCl decreases the adsorption of Ta-178 onto pertitanic acid from 99.8% to 1% but the K_{DW} is also very low with this eluent.

With ZrO_2 the adsorption of Ta decreases from 5% to 1% but the K_{DW} drops from 300 to 0.1 upon addition of 0.05% EDTA to 10^{-4}N HCl.

(1V) Fluoride

The influence of fluoride at varying acidity on the adsorption of W and Ta on MnO_2 , ZrO_2 and TiO_2 was studied by adding aqueous solutions of NaF, NaF + HNO_3 or NaF + NaNO_3 . W-178 was added as a fluoride complex. The results for MnO_2 are summarized in Figs. 1, 2. Fig. 1 lines (1) and (2) show that the combination of MnO_2 and dilute NaF solutions allows a separation of tantalum from tungsten. Although the volumes necessary to collect Ta-178 would be impractically large, it represents the first inorganic adsorbent-based system that has a high affinity for tungsten and lower affinity for tantalum. The K_{D} 's are not very much influenced by the concentration of NaF. Fig. 1, lines (3) and (4) depict the K_{D} of W and Ta as a function of fluoride concentration with 0.1M HNO_3 added.

Although HNO_3 is undesirable for human use, it is interesting to note that 0.1M HNO_3 did not influence the K_{D} for Ta or W at low fluoride concentrations, but does so more and more as the fluoride concentration increases. This could be effected by HF_2^- in the solution. Alternatively, the results may mean that cationic W and Ta species are formed which do not adsorb onto MnO_2 from an acidic medium where the adsorbent behaves as an anion exchanger.

Fig. 1, lines (5) and (6) show the K_{D} of W and Ta as a function of fluoride concentration with 0.1M NaNO_3 added. The adsorption of Ta is virtually unchanged while that of W is very much improved (compare lines (1) and (5)).

Fig. 2 shows the effect of variable NaNO_3 concentrations on the K_{D} for W and Ta at a constant 0.1% NaF concentration. It shows little effect of the nitrate concentration. Thus, the observed effect of Fig. 1, line (5) may be due to fluoride only, and the differences between line (1) and (5) reflect changes caused by NO_3^- on the adsorbent.

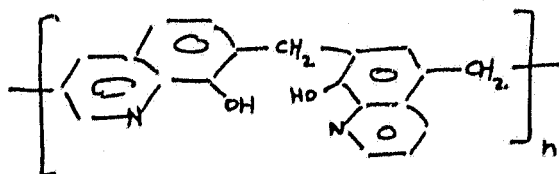
The poorer adsorption from HNO_3 containing solutions Fig. 1, lines (3) and (4) may reflect the lower con-

centration of ionic fluoride in acidic solutions and thus a tendency towards cationic W and Ta-species which would not adsorb onto MnO_2 , which has anion-exchange properties in acidic media.

II. Synthesis of chelate resins

a. Oxine-formaldehyde resin

Oxine - formaldehyde resin was synthesized according to a previously published procedure⁽⁴⁾. Oxine and formaldehyde were condensed by acid catalysis. The resulting polymer should



still be capable of forming chelates with metal ions and will be evaluated with W and Ta.

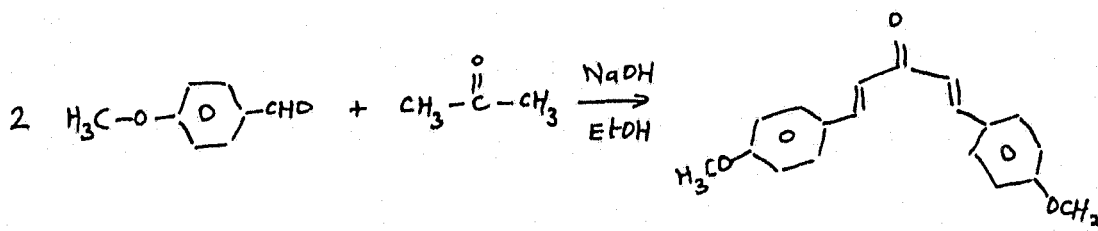
b. Benzoin oxime-formaldehyde

This resin could not be synthesized with the available facilities. High pressure and high temperature are probably needed to get the non-activated ring of L- benzoin oxime to react.

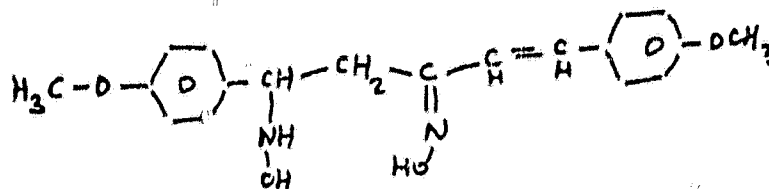
c. AMHOP-based resin

AMHOP (Anti-1,5-di-(p-methoxyphenyl)-1-hydroxylamino-3-oximino-4-pentene) reacts with WO_4^{2-} and its synthesis is presently under study. If it does differentiate well between W and Ta, it may be suitable to load the W-salt onto a Bio-Rad AG 1 x 8 column or to try to incorporate it into a chelating resin.

The synthesis of the intermediate compound anisalacetone has been conducted successfully.



Anisalacetone was reacted with hydroxylamine to try to form AMHOP (1,5-di-(p-methoxyphenyl)-1-hydroxylamino-3-oximino-4-pentene) recrystallization yielded yellow crystals (MP 127-128°C). The AMHOP structure



could not be confirmed by IR, NMR or elemental analysis. The final product is presumably the monoxime as confirmed by elemental analysis (Table 8) and the absence of field shift by the NHOH group close to the terminal methoxy groups.

TABLE 8

Elemental Analysis

Product	%N	%C	%H
AMHOP (calculated)	8.18	66.7	6.48
Monoxime (calculated)	4.53	73.8	6.19
Experimental	4.42	73.4	6.15

The monoxime itself reacts with WO_4^{2-} and K_D 's were determined between this product and 10^{-3}N HCl for W and Ta. They are 36 and 1.2, respectively. 94.5% of Ta-178 can be eluted from W-178 loaded monoxime but the K_{DW} is too low. Alternative eluents will be tested.

Efforts to synthesize the WO_4^{2-} -binding AMHOP led to the monoxime again.

This could be caused by a reverse addition of the reagents. Ammonium acetate should have been added to the dianisalacetone first for pH adjustment before hydroxylamine is added. The synthesis will be repeated.

D. WORK PLANNED IN THE NEXT SIX MONTHS

In the next six months the ongoing work will continue and some new possible avenues to a W-178/Ta-178 generator will be explored.

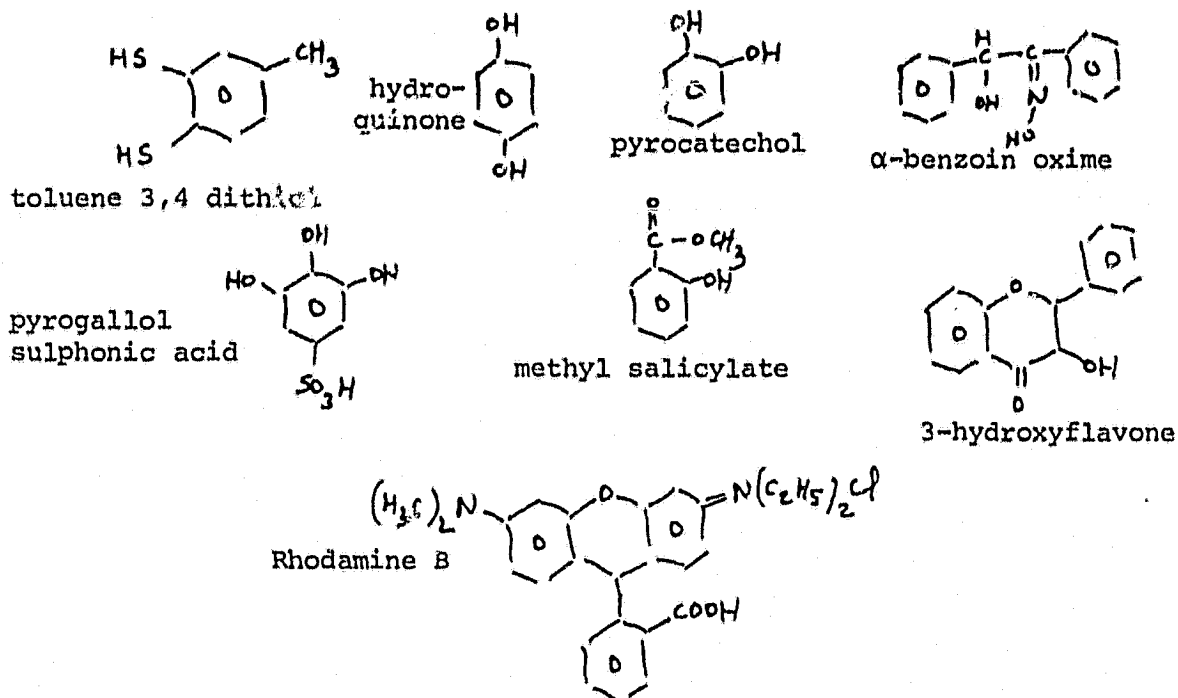
I. Tantalum-desorption

Tantalum-complexing agents will be tested for their ability to desorb ^{178}Ta from the adsorbents. Although not all of them would be acceptable as eluent additives a variety of organic complexants, like sodium oxalate, sodium tartrate and sodium citrate will be tried. The concentration of the complexant and the pH of the eluent will be varied within the limits imposed by the isotonicity and pH requirements for injectable solutions. Depending on the

stability constants between tungsten and tantalum and the organic complexants, conditions may be found under which tungsten is adsorbed more strongly and tantalum may be desorbed more easily.

II. Alternate synthetic adsorbents

Alternate inorganic chromatographic adsorbents for example insoluble tungstates will be evaluated. More chelate resins will be synthesized and tested for their ability to retain tungsten and eluate tantalum. Synthetic organic resins will be produced by condensing formaldehyde with known organic complexants for tungsten. Among these complexants toluene 3,4 dithiol, salicylfluorone and anthrafluorone are the most used. As tantalum itself is complexed well by polyphenolic compounds, the elution circumstances for ^{178}Ta from a generator will be carefully selected for the above mentioned chelate resins. Adsorption studies as a function of pH will need to establish the conditions for separating tungsten from tantalum on such resins. Some of the chelating agents that are being considered are:



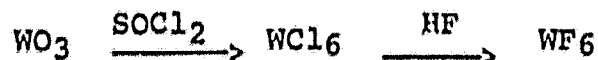
III. K_D-determinations

K_D-determinations will continue on synthetic adsorbents. Specifically, the oxime-formaldehyde and other synthetic chelate resins must be transformed in practical resins and the K_D's of W and Ta between these resins and various eluents determined.

The MnO₂/NaF system must be further evaluated, i.e., the charge of the ionic W and Ta-species in solution must be determined by electrophoresis of Ta-182 labelled solutions and possibly elemental analysis of isolated tantalum species. The ion exchange behaviour of MnO₂ in fluoride-nitrate media will be evaluated by means of cationic isotopes, e.g. ^{86}Rb .

IV. Distillation Generator

WF₆ (BP = 19.5°C) can easily be separated from Tantalum fluorides by volatilization. WF₆ can be produced by the following reaction



The W-178-WF₆ could presumably be separated from Ta-178 by using a simple 2-vessel evacuated container, one side of which would be kept at room temperature while the other side is dipped into an ice-salt mixture or CO₂-acetone mixture to freeze out the WF₆. The Ta-178 fluorides can subsequently be collected from the un-cooled vessel.

There are potential problems associated with this convenient approach:

- a. WF₆ is sensitive to hydrolysis: this could be minimized by the exclusion of H₂O from the system and using only thoroughly-dried vessels for collection and storage of the WF₆. Addition of carrier tungsten would also greatly help and have no impact on the Ta-178 product quality.
- b. WF₆ production may require special equipment and reagents: HF-gas is probably required to avoid WF₆-hydrolysis.
- c. WF₆ reacts with all metals except Au and Pt. Specially-designed vessels may be needed for its use. It is assumed that teflon will be acceptable.

E. REFERENCES

1. Neirinckx, R.D., Jones, A.G., Davis, M.A., et al, J. Nucl. Med. 19: 514-519, 1978.
2. Neirinckx, R.D. and Davis, M.A., Proceedings of 2nd Intern. Symp. Radiopharm, Seattle, Washington, p. 791-799, March 19-22, 1979.
3. Neirinckx, R.D. and Davis, M.A., J. Nucl. Med, 20: 1075-1079, 1979.
4. deGeiso, R.C. et al, J. Appl. Polymer Science, 9, 411, 1965.

FIG. 1

K_{D_W} AND $K_{D_{Ta}}$ AS f (NaF CONC.) BETWEEN MnO_2 AND SOLUTIONS OF NaF, NaF + HNO_3 OR NaF + $NaNO_3$

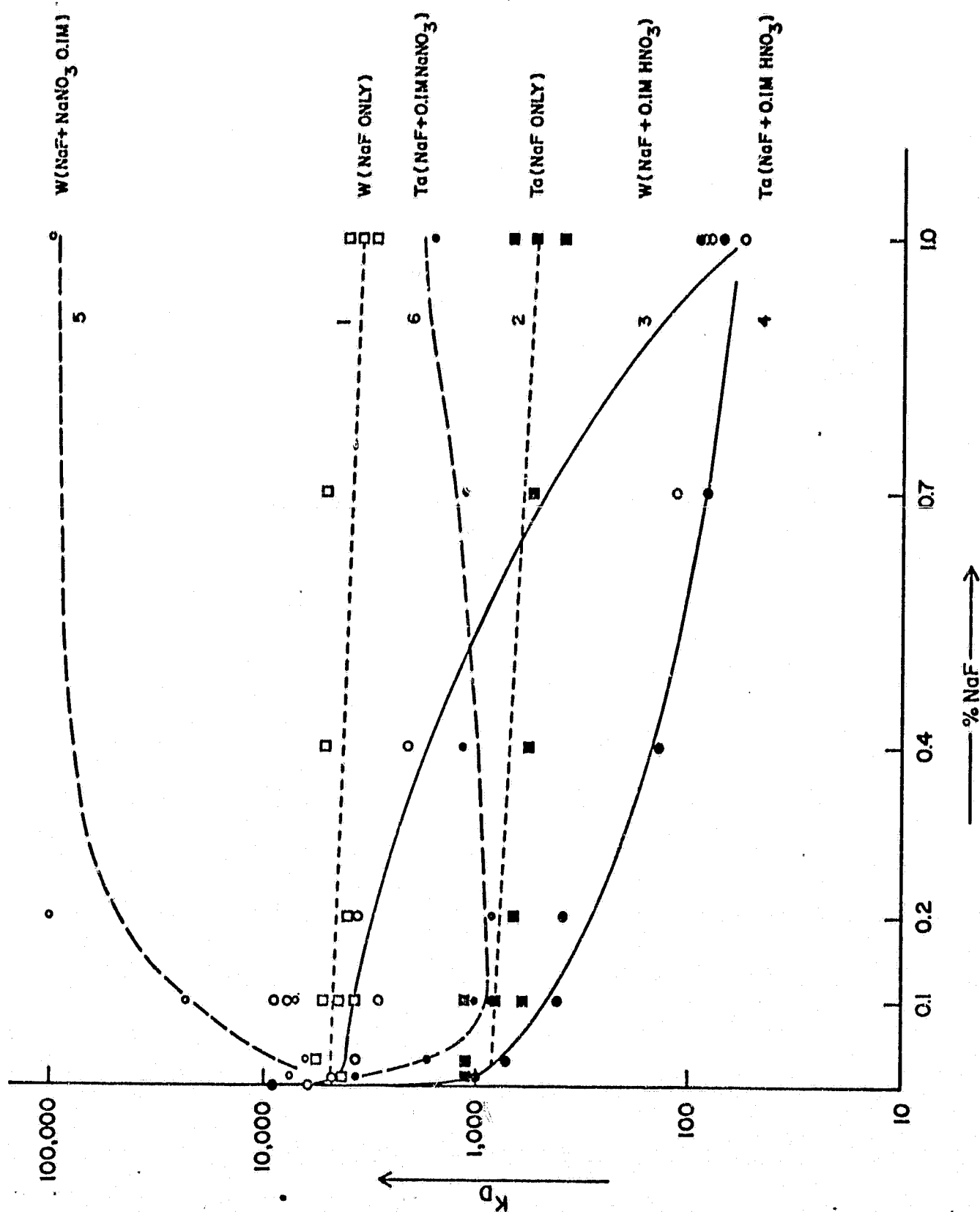
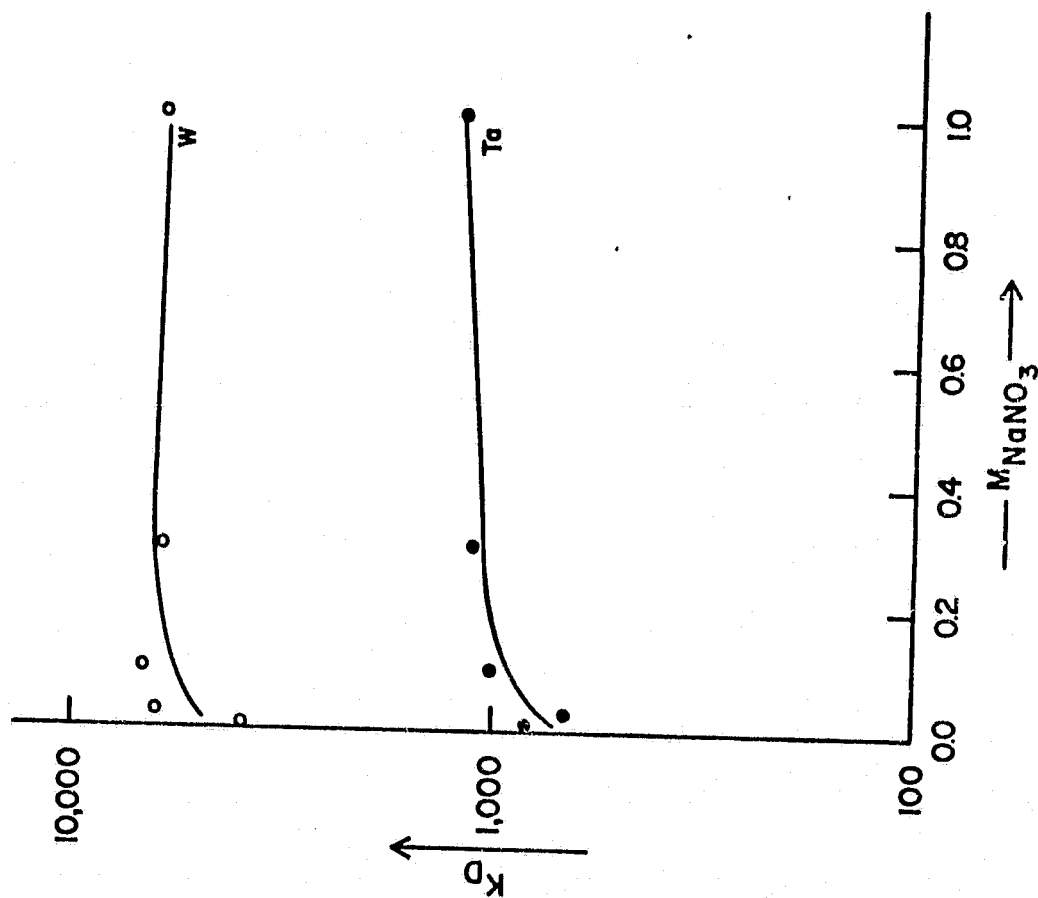


FIG. 2

K_{DW} AND K_{DTa} BETWEEN 0.1% NaF IN NaNO_3 SOLUTIONS AND MnO_2



Report, End of Year

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In the second half of the year, the stress was mainly on the use of complexing eluents because of the high affinity of hydrous oxides for tantalum, on the synthesis of chelate resins and on the use of novel techniques (electrolytic) to solve the tantalum-adsorption problem.

B. MATERIALS AND METHODS

The following chromatographic inorganic adsorbents were supplied by Applied Research (Brussels, Belgium); hydrous titanium oxide, titanium oxide hydrogen peroxide hydrate, hydrous zirconium oxide, hydrous ferric oxide, hydrous stannic oxide, polyantimonic acid, silicic acid, hydrous chromium oxide, hydrous manganese dioxide, zirconium phosphate, tin phosphate, Phomix (20% ammonium phosphotungstate in zirconium phosphate), Siphosir (zirconium phosphate-silicate), chromium phosphate, titanium phosphate, molybdenyl ferrocyanide, zirconium ferrocyanide, ferric ferrocyanide and K-Co ferrocyanide. Alumina was obtained from Woelm (Eschwege, Germany), Tungsten carbide, non-chromatographic, was obtained from Pfaltz and Bauer (Stamford, Conn.) Tungsten disulfide was obtained from Alfa-Ventron (Danvers, Mass.). Bio-Rex G and Bio-Rad AG 3x4 A were obtained from Bio-Rad (Richmond, Cal.), Amberlite CG-400 from Mallinckrodt (St. Louis, Mo.) and diethyl aminoethyl cellulose DE-32 from Whatman (Clifton, N.J.).

Other inorganic materials were synthesized by us. They included tungstic acid (WO_3); CaF_2 and SrF_2 -coated Al_2O_3 ; anhydrous SnO_2 , TiO_2 , SiO_2 , CrO_3 , MnO_2 , Tin phosphate, zirconium phosphate, titanium phosphate, molybdenyl ferrocyanide, zirconium ferrocyanide and ferric ferrocyanide. Tungstic acid adsorbent was produced by heating WO_3 with a B_2O_3 flux to $1,200^\circ\text{C}$, cooling the melt to 800°C at a rate of $2^\circ\text{C}/\text{hour}$ and then uncontrolled to room temperature. CaF_2 and SnF_2 coated Al_2O_3 were prepared by treatment with a NaF solution of a Al_2O_3 adsorbent that had been saturated with Ca^{2+} or Sr^{2+} by equilibration of the adsorbent with concentrated solutions of CaCl_2 or SrCl_2 , respectively.

The anhydrous inorganic materials were prepared by heating the corresponding aqueous materials in a nickel crucible until H_2O -evolution ceased. A SnO_2 -adsorbent with lower adsorptivity was obtained by saturating the adsorption sites with $\text{Ca}(\text{II})$. The synthetic chelate resins included a pyrogallol-formaldehyde resin, which had been reported earlier (2) and experimental resins formed by copolymerisation of alphabenzoin oxime or AMHOP (anti-1,5-di(p-methoxyphenyl)-1-hydroxylamine-3-oximino-4-pentene) with formaldehyde only the pyrogallol-formaldehyde resin is presently in a form suitable for column use.

Most development work has involved the measurement by batch equilibration of the K_D values of W and Ta between these adsorbents and various mobile phases of interest. The first adsorbent was preequilibrated three times with the liquid phase, and the supernate decanted. The batch equilibration was carried out using 100 mgr of adsorbent and 5 grams of mobile phase, to which a ^{178}W - ^{178}Ta mixture was added. The two phases were then shaken for 5 minutes by means of a Hematec Aliquot mixer. After centrifugation, samples from each phase were analyzed for ^{178}W and ^{178}Ta by means of a $\text{Ge}(\text{Li})$ detector coupled to an ND60 γ -spectrophotometer.

^{178}Ta was quantitated using its 93 kev gamma-ray. After correction for physical decay, the K_D -values for tantalum were calculated as described previously (3). ^{178}W is quantitated after both fractions are allowed to decay for 90 minutes and by counting the equilibrium activity of ^{178}Ta associated with the ^{178}W . The K_D -values are calculated as for tantalum.

The following non-complexing eluents were evaluated: 10^{-3}N HCl , H_2O , 0.1N NaOH , 0.25% $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$, 0.7% NaCl + 0.2% NaHCO_3 , 0.9% NaCl and 0.1% NaHSO_3 .

As complexing eluents citric acid, sodium citrate solutions, sodium fluoride solutions of varying acidity, EDTA and ascorbic acid were evaluated.

C. SUMMARY OF RESULTS AND DISCUSSION

I. K_D -determinations

a. Non-complexing eluents/Inorganic adsorbents

A radioisotope generator should display a strong adsorption of the mother isotope (W-178) and a weak adsorption for the daughter isotope (Ta-178).

A summary of the results with the evaluated inorganic adsorbent/non-complexing eluent combinations is given in Tables 1-3. Table 1 summarizes the results for adsorbents that have a high affinity for tantalum, Table 3 for the adsorbents that have a low affinity for tungsten and Table 3 for the adsorbents that have a high affinity for both tungsten and tantalum. As can be seen from these tables, the use of non-complexing eluents combined with inorganic adsorbents does not lead to an acceptable W-178/Ta-178 generator system.

TABLE 1

K_D of tantalum between various eluents and inorganic adsorbents with a high affinity for tantalum

Absorbent/ Mobile phase	$10^{-3}N$ HCl	H_2O	0.1N NaOH	0.25% PO_4^{3-}	0.7% NaCl 0.2% $NaHCO_3$	0.9% NaCl	0.1% $NaHSO_3$
TiO_2	>200	>150	>30	>60	>80	>150	>300
$SnO_2(CaCl_2)$	>200		>40	>200		>250	
Zr(ferrocy)	>250		>50				
Ni(ferrocy)	>200		>70				
Ti(ferrocy)	>300		>90				
K-Co(ferrocy)	>300		>180	>60		>70	
SnO_2 (heated)	>60		>45				
$SnO_2/CaCl_2$	>200		>40	>200			>250
WS_3	>100						>100

TABLE 2

K_D values of W between various eluents and inorganic adsorbents with low affinity for tungsten

Adsorbent/ Mobile phase	$10^{-3}N$ HCl	H_2O	0.1N NaOH	0.25% PO_4^{3-}	0.7% NaCl 0.2% $NaHCO_3$	0.9% NaCl	0.1% $NaHSO_3$
SnO_2	30	68	41	6	5	120	18
SiO_2	27		7			3	
Neutral Al_2O_3	30		6	8			
CrO_3	2		2	3		3	
Zr-phosph	15	44	16	89	55	96	55
Sn-phosph	4	14	8	51	28	78	35
tungsten carbide	5		1	36	6	12	24
Phomix		34	17				
Siphozir		53	12				
Cr-phosph	3		4				
Cu-ferrocy	8		10				
MoO_2 (ferrocy)	7						
TiO_2	95	110	10	17	21		
Al_2O_3/CaF_2	3		3	6		28	
Al_2O_3/SrF_2	6		8	15		20	
WS_3			2	24	2		6

TABLE 3

K_D values for W and Ta between various eluents and inorganic adsorbents with a high affinity for both elements

Adsorbent/ Eluent	$10^{-3}N$ HCl	H ₂ O	0.1N NaOH	0.25% PO ₄ ³⁻	0.7% NaCl + 0.2% NaHCO ₃	0.9% NaCl	0.1% NaHSO ₃
TiO ₂ .H ₂ O ₂ / K _{DW}	>2500	>500	59	>1300	>1300	>1300	>1000
K _{DTa}	>200	>400	>140	>300	>300	>350	>300
Fe ₂ O ₃ /K _{DW}	>2400	>1000		>125		>800	>800
K _{DTa}	>500	>250		>125		>200	>170
Sb ₂ O ₅ /K _{DW}	>250			>600	>900	>900	>800
K _{DTa}	>100			>200	>200	>200	>200
MnO ₂ /K _{DW}	2100		95	800		5600	
K _{DTa}	>350		>200	>300		>800	
Ti-phosph/ K _{DW}	275		140	380		1100	
K _{DTa}	>150		>110	>200		>200	
Fe(III)/ ferrocyl/ K _{DW}	1500		125	470		800	
K _{DTa}	>140		>140	>90		>60	
ZrO ₂ /K _{DW}	>100	>400				>250	>250
K _{DTa}	>200	>100				>50	>50

b. Non-complexing eluents/organic adsorbents

1. Commercially-available adsorbents

The organic adsorbents AG 3x4A, CG-400 and DE-32 all have a high affinity for tantalum.

The K_D -value of W between 0.01N HCl, 0.1N HCl or 0.5N HCl and Bio-Rex 9 was 71, 61 and 35, respectively. This adsorbent had a low affinity for tantalum.

2. Synthetic results

The K_D -values for W and Ta between the synthetic chelate resin pyrogallol-formaldehyde and aqueous solutions of differing pH are summarized in Table 4.

TABLE 4

K_D values for W and Ta between pyrogallol-formaldehyde and aqueous phases of variable pH

pH mobile phase	1	2	3	4	5	6	7	11
K_{DW}	10	8	8	6	80	70	60	60
K_{DTa}	>50	>50	>50	>50	>50	>50	>50	>50

3. Anhydrous adsorbents

It is well known that metal oxides have a high affinity for elements which hydrolyze easily.

The influence of hydration water of the adsorbents on the adsorption of tantalum-178 was evaluated by substitution of CH_3OH for H_2O in desorption studies from ZrO_2 with 10^{-2} - 10^{-5} N HCl.

Using aqueous solutions, the % Ta-desorption was 1%-10% with 10^{-5} N - 10^{-2} N HCl. Using methanolic solutions, the yields were 70-90% with 10^{-5} - 10^{-2} N HCl, 70% with pure methanol. The K_{DW} was 6,000-2,500 for 10^{-5} - 10^{-2} N HCl.

This indicates that reaction of the highly activated tantalum species, formed by W-178 decay react with water to yield strongly-adsorbing species. The adsorption characteristics of dehydrated metal oxides was studied next. The K_D values for W between the hydrous oxides or the heated "anhydrous" oxides and various aqueous solutions are given in Table 5. Adsorption as well as desorption values are given from the HCl 0.1N + H_2O_2 0.1% solution.

TABLE 5

K_{DW} between hydrous and anhydrous adsorbents and various aqueous eluents

Adsorbent	K_{DW}		K_{DW} 5% glucose solution	1% Sodium tetraphenyl borate solution
	ADS. HCl 0.1N + H_2O_2	DES. 0.1%		
hydrous TiO_2	22,000	17,500	10,000	>20,000
TiO_2 heated	6,000	11,000	9,000	14,000
hydrous Zr-Si- PO_4	1	190		
Zr-Si- PO_4	1	150		
hydrous Ti-phosph	11	120	400	1,500
Ti-heated	4	65		
hydrous SnO_2	610	11,000	3,800	8,000
SnO_2 heated	160	280		
hydrous ZrO_2	825	1,550	1,500	7,000
ZrO_2 heated	dissolves			
hydrous SiO_2	7	17		
SiO_2 heated	9	27		

In nearly all cases the anhydrous adsorbents have less affinity for tungsten. However, in all cases the K_D 's for tantalum were higher than for tungsten, and as such none of the heated adsorbents is suitable as a support for a W-178/Ta-178 generator when used with a non-complexing eluent.

When using the non-complexing eluents of all the previous studies, most of the evaluated adsorbents display a strong affinity for tantalum. The balance of the solid phases adsorb tungsten too weakly to be of practical value.

The reason for the strong tantalum binding may be that most of the adsorbents are either metal oxides or phosphates. The tantalum $5d$ -orbitals overlap strongly with oxygen $2p$ -orbitals to give substantial π -bonding. The initial protonated species of the resultant tantalum oxides can expand their coordination sphere by coordinating water molecules. Since most of our adsorbents studied are hydrates, this could have led to the strong tantalum binding. Tantalum -178, separated from W-178 by using an earlier-published procedure (1) was used to evaluate whether the binding of tantalum onto the adsorbents is irreversible. A phosphate-buffered solution of tantalum-178 was equilibrated with ZrO_2 , the K_D measured and the adsorbent subsequently reequilibrated with fresh eluent. The K_D for the desorption was compared with the adsorption values as a function of the phosphate buffer concentration. For sodium phosphate concentrations between 0.1% and 0.25% the K_{DTa} for adsorption was 4, while by desorption it was 1,600. This demonstrates the irreversibility of the tantalum adsorption or the slow kinetics of its desorption. Since the tantalum -178 is carrier-free it is very unlikely that polymeric species, e.g., $Ta_6O_{18}^{6-}$ are involved in the binding.

The problems encountered may also be caused by the chemical composition of the W-178 compound loaded onto the adsorbents. Isoelectronic transition of the W-178 probably does not break any chemical bonds between the daughter isotope Ta-178 and the atoms or groups of the molecule. Most of the experiments have been carried out with WO_4^{2-} so that the resultant tantalum species may be expected to be oxygenated. Therefore, experiments with fluoride-complexes of tungsten were carried out. It is also planned to evaluate other W-complexes. The choice of the complexant should be such that the evolving tantalum-complex is stable and possibly without affinity for inorganic adsorbents. These tungsten-complexes will only be stable in solutions containing the complexant.

b. Complexing eluents/inorganic adsorbents

1. Altered adsorbents

Citrate was evaluated first as a complexant for W and Ta. To insure that sufficient complexant be available, the studied inorganic adsorbents were heated with an aqueous

saturated sodium citrate solution before use in K_D determinations. Equilibration was then carried out between W-178 containing 1% sodium citrate solutions and the respective pretreated adsorbents. The K_D -values for W are summarized in Table 6.

TABLE 6

Adsorbent*	K_{DW}
Phozir A	<1
Ti-phosphate (anhydrous)	<1
TiO ₂ (anhydrous)	60
TiO ₂	<1
SnO ₂	<1
Ti-phosphate	<1
SnO ₂ (anhydrous)	<1

* pretreated with citrate

The adsorption of W was negligible in nearly all cases, which makes these pretreated adsorbents unacceptable for the W-178/Ta-178 generator.

2. Commercially available adsorbents

The influence of the addition of complexants to the eluents on the adsorption of tungsten on the inorganic adsorbents was studied.

(1) Citric acid

0.01% citric acid was added to various eluents used with ZrO₂ and pertitanic acid. The results are shown in Table 7.

TABLE 7

Eluent	K_{DW} on	
	SrO ₂	Sb ₂ O ₅
10 ⁻³ N HCl	>100	>250
10 ⁻³ N HCl + citric acid	500	30
Saline 0.9%	>250	>900
Saline + citric acid	60	150
H ₂ O	>400	
H ₂ O + citric acid	340	

Addition of citric acid generally lowered tungsten adsorption, but in all cases the K_{DTa} was higher than K_{DW} .

(11) Ascorbic acid

Increasing amounts of ascorbic acid were added to 10⁻⁴N HCl eluent in combination with ZrO₂ or pertitanic acid. For ascorbic acid concentrations between 0 and 0.05% the percent tantalum eluted from ZrO₂ or pertitanic acid was constant and was 95% by adsorption

and 10% by desorption for SnO_2 , and 70% by adsorption and 0.1% by desorption for pertitanic acid.

(11.1) EDTA

Addition of 0.05% EDTA to 10^{-4}N HCl decreases the adsorption of Ta-178 onto pertitanic acid from 99.8% to 1% but the K_{DW} is also very low with this eluent.

With ZrO_2 the adsorption of Ta decreases from 5% to 1% but the K_{DW} drops from 300 to 0.1 upon addition of 0.05% EDTA to 10^{-4}N HCl.

(1V) Fluoride

The influence of fluoride at varying acidity on the adsorption of W and Ta on MnO_2 , ZrO_2 and TiO_2 was studied by adding aqueous solutions of NaF, NaF + HNO_3 or NaF + NaNO_3 . W-178 was added as a fluoride complex. The results for MnO_2 are summarized in Figs. 1, 2. Fig. 1 lines (1) and (2) show that the combination of MnO_2 and dilute NaF solutions allows a separation of tantalum from tungsten. Although the volumes necessary to collect Ta-178 would be impractically large, it represents the first inorganic adsorbent-based system that has a high affinity for tungsten and lower affinity for tantalum. The K_{D} 's are not very much influenced by the concentration of NaF. Fig. 1, lines (3) and (4) depict the K_{D} of W and Ta as a function of fluoride concentration with 0.1M HNO_3 added.

Although HNO_3 is undesirable for human use, it is interesting to note that 0.1M HNO_3 did not influence the K_{D} for Ta or W at low fluoride concentrations, but does so more and more as the fluoride concentration increases. This could be effected by HF_2^- in the solution. Alternatively, the results may mean that cationic W and Ta species are formed which do not adsorb onto MnO_2 from an acidic medium where the adsorbent behaves as an anion exchanger.

Fig. 1, lines (5) and (6) show the K_{D} of W and Ta as a function of fluoride concentration with 0.1M NaNO_3 added. The adsorption of Ta is virtually unchanged while that of W is very much improved (compare lines (1) and (5)).

Fig. 2 shows the effect of variable NaNO_3 concentrations on the K_{D} for W and Ta at a constant 0.1% NaF concentration. It shows little effect of the nitrate concentration. Thus, the observed effect of Fig. 1, line (5) may be due to fluoride only, and the differences between line (1) and (5) reflect changes caused by NO_3^- on the adsorbent.

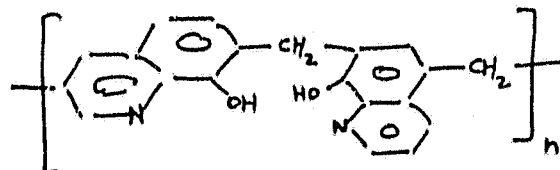
The poorer adsorption from HNO_3 containing solutions Fig. 1, lines (3) and (4) may reflect the lower con-

centration of ionic fluoride in acidic solutions and thus a tendency towards cationic W and Ta-species which would not adsorb onto MnO_2 , which has anion-exchange properties in acidic media.

II. Synthesis of chelate resins

a. Oxine-formaldehyde resin

Oxine - formaldehyde resin was synthesized according to a previously published procedure⁽⁴⁾. Oxine and formaldehyde were condensed by acid catalysis. The resulting polymer should



still be capable of forming chelates with metal ions and will be evaluated with W and Ta.

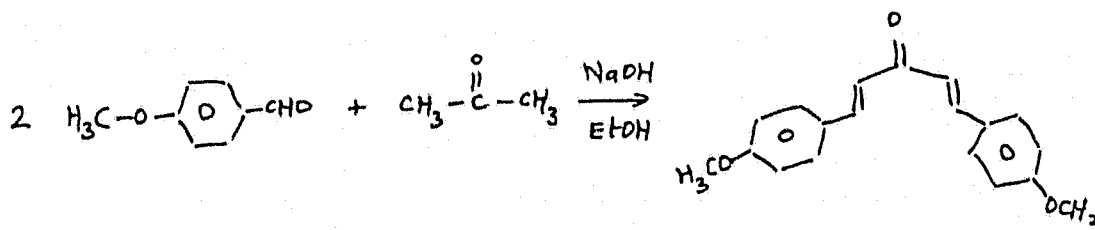
b. Benzoin oxime-formaldehyde

This resin could not be synthesized with the available facilities. High pressure and high temperature are probably needed to get the non-activated ring of L- benzoin oxime to react.

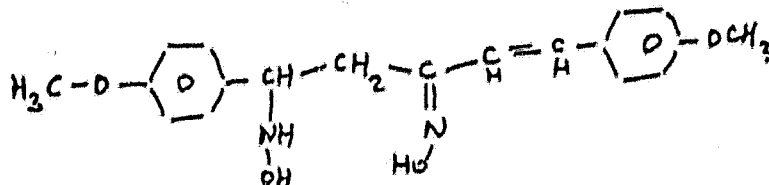
c. AMHOP-based resin

AMHOP (Anti-1,5-di-(p-methoxyphenyl)-1-hydroxylamino-3-oximino-4-pentene) reacts with WO_4^{2-} and its synthesis is presently under study. If it does differentiate well between W and Ta, it may be suitable to load the W-salt onto a Bio-Rad AG 1 x 8 column or to try to incorporate it into a chelating resin.

The synthesis of the intermediate compound anisalacetone has been conducted successfully.



Anisalacetone was reacted with hydroxylamine to try to form AMHOP (1,5-di-(p-methoxyphenyl)-1-hydroxylamino-3-oximino-4-pentene) recrystallization yielded yellow crystals (MP 127-128°C). The AMHOP structure



could not be confirmed by IR, NMR or elemental analysis. The final product is presumably the monoxime as confirmed by elemental analysis (Table 8) and the absence of field shift by the NHOH group close to the terminal methoxy groups.

TABLE 8

Elemental Analysis

Product	%N	%C	%H
AMHOP (calculated)	8.18	66.7	6.48
Monoxime (calculated)	4.53	73.8	6.19
Experimental	4.42	73.4	6.15

The monoxime itself reacts with WO_4^{2-} and K_D 's were determined between this product and 10^{-3}N HCl for W and Ta. They are 36 and 1.2, respectively. 94.5% of Ta-178 can be eluted from W-178 loaded monoxime but the K_{DW} is too low. Alternative eluents will be tested.

Efforts to synthesize the WO_4^{2-} -binding AMHOP led to the monoxime again.

This could be caused by a reverse addition of the reagents. Ammonium acetate should have been added to the dianisalacetone first for pH adjustment before hydroxylamine is added. The synthesis will be repeated.

D. WORK PLANNED IN THE NEXT SIX MONTHS

In the next six months the ongoing work will continue and some new possible avenues to a W-178/Ta-178 generator will be explored.

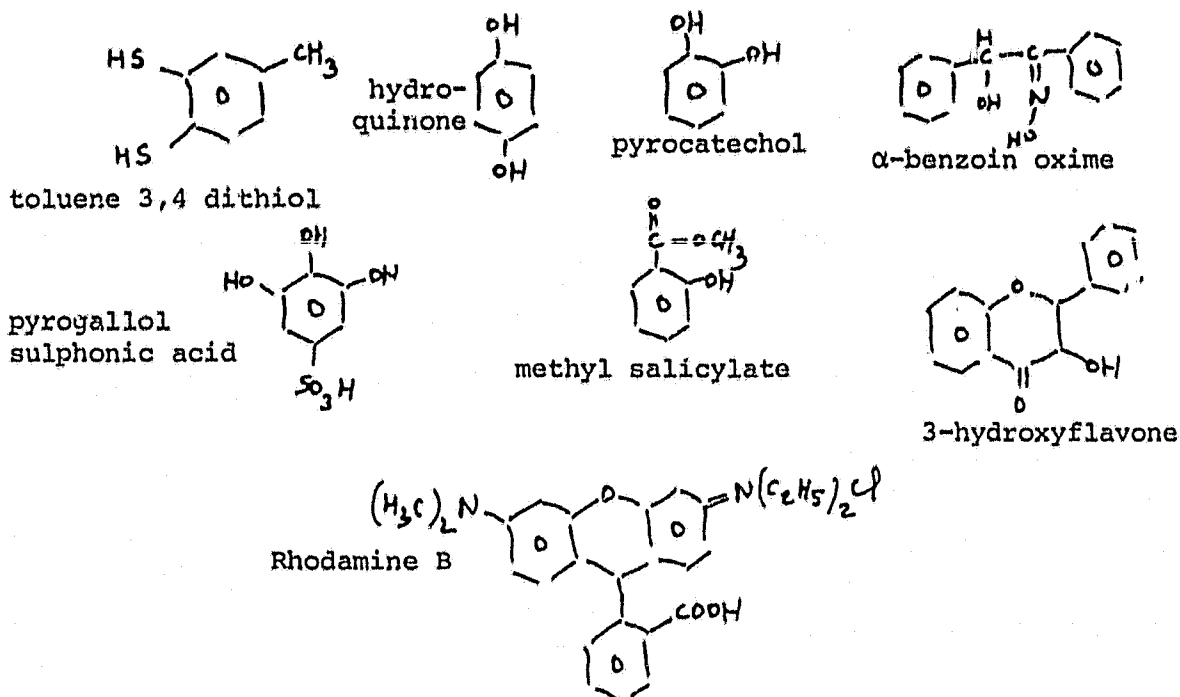
I. Tantalum-desorption

Tantalum-complexing agents will be tested for their ability to desorb ^{178}Ta from the adsorbents. Although not all of them would be acceptable as eluent additives a variety of organic complexants, like sodium oxalate, sodium tartrate and sodium citrate will be tried. The concentration of the complexant and the pH of the eluent will be varied within the limits imposed by the isotonicity and pH requirements for injectable solutions. Depending on the

stability constants between tungsten and tantalum and the organic complexants, conditions may be found under which tungsten is adsorbed more strongly and tantalum may be desorbed more easily.

II. Alternate synthetic adsorbents

Alternate inorganic chromatographic adsorbents for example insoluble tungstates will be evaluated. More chelate resins will be synthesized and tested for their ability to retain tungsten and eluate tantalum. Synthetic organic resins will be produced by condensing formaldehyde with known organic complexants for tungsten. Among these complexants toluene 3,4 dithiol, salicylfluorone and anthrafluorone are the most used. As tantalum itself is complexed well by polyphenolic compounds, the elution circumstances for ^{178}Ta from a generator will be carefully selected for the above mentioned chelate resins. Adsorption studies as a function of pH will need to establish the conditions for separating tungsten from tantalum on such resins. Some of the chelating agents that are being considered are:



III. K_D -determinations

K_D -determinations will continue on synthetic adsorbents. Specifically, the oxine-formaldehyde and other synthetic chelate resins must be transformed in practical resins and the K_D 's of W and Ta between these resins and various eluents determined.

The MnO_2/NaF system must be further evaluated, i.e., the charge of the ionic W and Ta-species in solution must be determined by electrophoresis of Ta-182 labelled solutions and possibly elemental analysis of isolated tantalum species. The ion exchange behaviour of MnO_2 in fluoride-nitrate media will be evaluated by means of cationic isotopes, e.g. ^{86}Rb .

IV. Distillation Generator

WF₆ (BP = 19.5°C) can easily be separated from Tantalum fluorides by volatilization. WF₆ can be produced by the following reaction



The W-178-WF₆ could presumably be separated from Ta-178 by using a simple 2-vessel evacuated container, one side of which would be kept at room temperature while the other side is dipped into an ice-salt mixture or CO₂-acetone mixture to freeze out the WF₆. The Ta-178 fluorides can subsequently be collected from the un-cooled vessel.

There are potential problems associated with this convenient approach:

- a. WF₆ is sensitive to hydrolysis: this could be minimized by the exclusion of H₂O from the system and using only thoroughly-dried vessels for collection and storage of the WF₆. Addition of carrier tungsten would also greatly help and have no impact on the Ta-178 product quality.
- b. WF₆ production may require special equipment and reagents: HF-gas is probably required to avoid WF₆-hydrolysis.
- c. WF₆ reacts with all metals except Au and Pt. Specially-designed vessels may be needed for its use. It is assumed that teflon will be acceptable.

E. REFERENCES

1. Neirinckx, R.D., Jones, A.G., Davis, M.A., et al, J. Nucl. Med. 19: 514-519, 1978.
2. Neirinckx, R.D. and Davis, M.A., Proceedings of 2nd Intern. Symp. Radiopharm, Seattle, Washington, p. 791-799, March 19-22, 1979.
3. Neirinckx, R.D. and Davis, M.A., J. Nucl. Med, 20: 1075-1079, 1979.
4. deGeiso, R.C. et al, J. Appl. Polymer Science, 9, 411, 1965.

FIG. 1

K_{D_W} AND $K_{D_{Ta}}$ AS f (NaF CONC.) BETWEEN MnO_2 AND SOLUTIONS OF NaF, NaF+ HNO_3 OR NaF+ $NaNO_3$

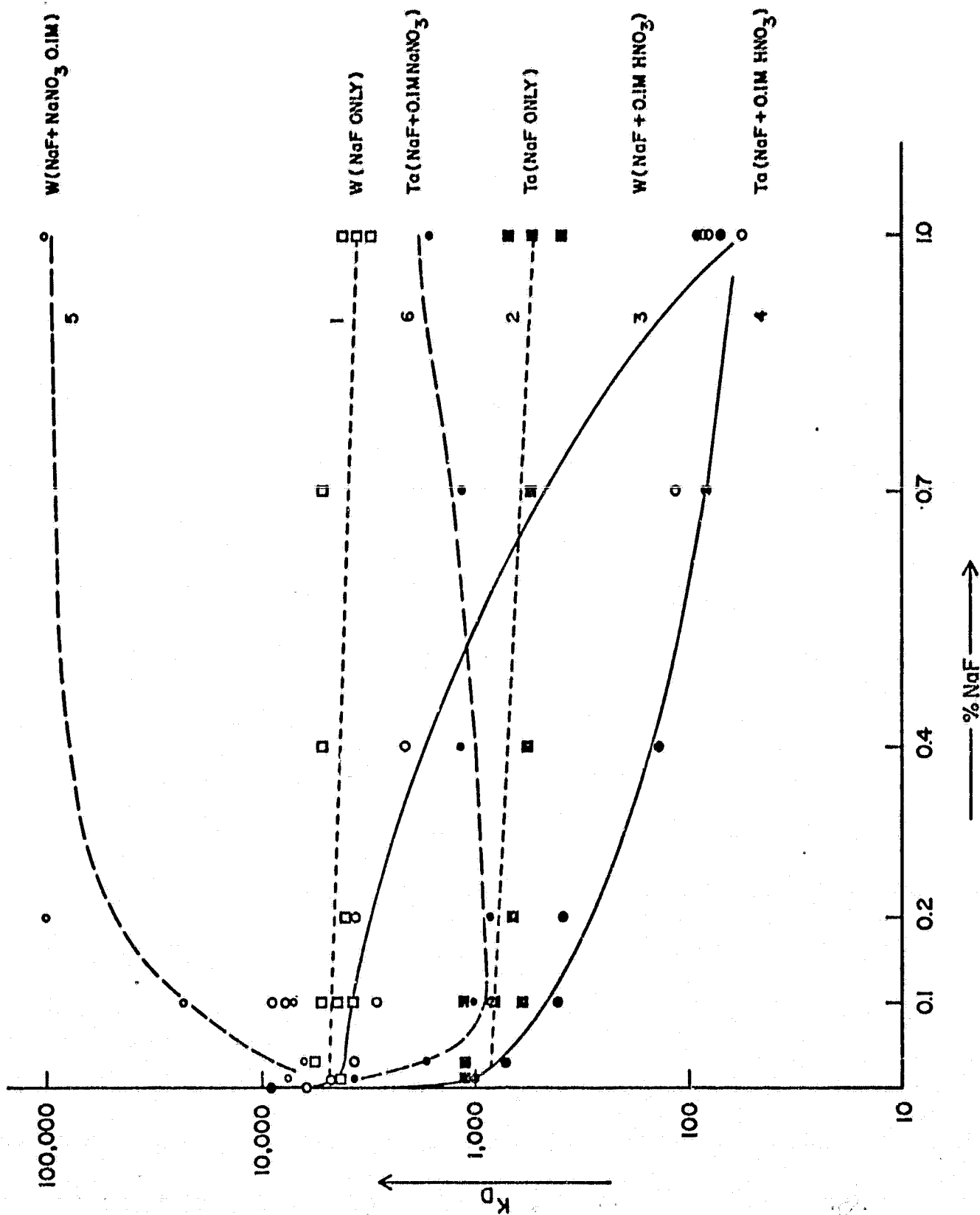


FIG. 2

K_{D_W} AND $K_{D_{Ta}}$ BETWEEN 0.1% NaF IN NaNO_3 SOLUTIONS AND MnO_2

